IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	09/622,816	Confirmation No.: 4693
Applicant	:	Weinberg	
Filed	:	July 17, 2001	
TC/A.U.	:	1615	
Examiner	:	Kishore, Gollamudi	
For	:	LIPID EMULSIONS IN THE TREATMENT OF SYSTEMIC POISONING	
Docket No.	:	69-06	
Customer No.	:	23713	

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May 15, 2006

/bkroge/

Date B. Kroge

AMENDMENT AND RESPONSE TO OFFICE ACTION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action mailed, November 15, 2005, Applicants respectfully request reconsideration of the rejection and entry of this Amendment. Please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims:

The listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1 – 2 (canceled)

3. (previously presented) The method of claim 27 wherein the oil is selected from the group consisting of monogylcerides, diglycerides, triglycerides, and mixtures thereof.

4. (previously presented) The method of claim 27 wherein the oil is a plant oil.

5. (previously presented) The method of claim 4 wherein the plant oil is selected from the group consisting of soybean oil, cotton seed oil, safflower oil, corn oil, coconut oil, sesame oil, peanut oil, olive oil, and mixtures thereof.

6. (previously presented) The method of claim 27 wherein the oil is selected from the group consisting of soybean oil, fish oil, animal oil, mineral oil, and chemically-synthesized oil.

7. (canceled)

8. (previously presented) The method of claim 27 wherein the emulsifier is a phospholipid.

9 – 11 (canceled)

12. (previously presented) The method of claim 8 wherein the phospholipid is selected from the group comprising of egg yolk phospholipids, hydrogenated egg yolk phosphor lipids, soybean phospholipids, hydrogenated soybean phospholipids, and mixtures thereof.

13 – 15 (canceled)

16. (previously presented) The method of claim 27 wherein the emulsifier is a lecithin.

17. (canceled)

18. (previously presented) The method of claim 27 wherein the tonicity modifier is selected from the group consisting of glycerin, sorbital, polyoxyethylated hydrocarbons, and C_6-C_{20} saturated or unsaturated aliphatic acids.

19 – 20 (canceled)

21. (previously presented) The method of claim 27 wherein the tonicity modifier comprises glycerin.

22 – 24 (canceled)

25. (previously presented) The method of claim 27 wherein the emulsion comprises particles in the range of about 0.25 microns to about 0.75 microns in diameter.

26. (canceled)

27. (currently amended) A method for <u>treating cardiotoxicity caused by a lipophilic or amphiphilic anesthetic agent</u> ~~removing a toxin from the circulation~~ which

comprises infusing a lipid emulsion composition intravenously whereby the ~~toxin~~ anesthetic agent permeates the lipid emulsion composition and is withdrawn from the bloodstream, said ~~liquid~~ lipid emulsion comprising essentially of an oil, an emulsifier, a tonicity modifier, and water, wherein the oil is present in an amount in the range of about 10 to about 30 percent by weight, the water is present in an amount in the range of about 70 to about 90 percent by weight, and the emulsifier is present in an amount in the range of about 1 percent to about 5 percent by weight.

28. (previously presented) The method of claim 27 wherein the lipid emulsion composition comprises about 20 weight percent soybean oil, about 2 weight percent glycerin, and about 1 weight percent egg yolk phospholipids, and about 80 weight percent water.

29. (previously presented) The method of claim 27 wherein the lipid emulsion composition is intravenously infused at an initial rate in the range of about 7.5 milliliters per kilogram per minute for a time period of about 30 seconds followed by a steady-state rate in the range of about 3 milliliters per kilogram per minute for a time period of about 2 minutes.

30 – 36 (canceled)

37. (currently amended) The method of claim ~~36~~ 27 wherein the anesthetic agent is selected from the group consisting of bupivacaine, lidocaine, tetracaine, and etidocaine~~, and alcohol~~.

38 – 39 (canceled).

REMARKS/ARGUMENTS

The present application contains claims 3-6, 8, 12, 16, 18, 21, 22, 24, 25, 27-29 and 36-39. Claim 27 is an independent claim and all the other claims depend from claim 27. Claims 27 and 37 are hereby amended, and claims 22, 24, 36, 38 and 39 are canceled.

Claim 27 is amended to recite a method for treating cardiotoxicity caused by anesthetic agents. Support for this amendment can be found on page 2, lines 26-29, page 3, lines 1-3, and Example 2 on pages 10-11 of the specification as filed. Claim 27 is also amended to recite a lipid emulsion composition comprising essentially of about 10 to about 30 percent by weight of an oil, about 1 to about 5 percent by weight of an emulsifier, about 70 to about 90 percent by weight of water, and a tonicity modifier. Support for this amendment can be found on page 5, lines 16-23, of the specification as filed. Claim 37 is amended to correct the claim dependency and to remove alcohol from the list of anesthetic agents.

I. Rejections under 35 U.S.C. 112

The Office Action mailed November 15, 2005 rejects the claims under 35 U.S.C. 112, first paragraph. The Examiner alleges that the specification, while enabling for the removal of bupivacaine, is not enabling for generic emulsions and toxins. Specifically, the Examiner asserts that just because a specific lipid was able to remove some of the circulating bupivacaine, one would not expect an emulsion containing any lipid to remove any toxin from circulation.

Claim 27 as amended recites a lipid emulsion having a specific range of an oil (10-30% by weight), emulsifier (1-5% by weight), and water (70-90% by weight). Additionally, claim 27 as amended recites a method of treating cardiotoxicity caused by lipophilic or amphiphilic anesthetic agents. Anesthetic agents are well known compounds in the art having effects, such as depression of the respiratory and cardiac systems, that are also well known in the art.

Bupivacaine is a common anesthetic agent administered to patients, which sometimes causes accidental death due to cardiac arrest. Example 1 of the specification illustrates that rats pre-treated with the lipid emulsions of the present invention are less susceptible to bupivacaine induced asystole. Example 2 further illustrates that rats given a lethal dose of bupivacaine can be resuscitated by administration of the lipid emulsion. Submitted with this Amendment is a declaration from one of the inventors, Dr. Guy Weinberg, stating that similar results were observed in studies using bupivacaine administered to dogs. The declaration also presents evidence that the method of the present invention has already been successfully tried, including by individuals other than the inventors, with other anesthetic agents such as ropivacaine, prilocaine, mepivacaine, and cocaine. The results of these additional examples are consistent with the results predicted with the bupivacaine experiments. Some of these additional examples include instances of resuscitation of human patients. Based on the experiments described in the specification, which have been supported in subsequent experiments, one skilled in the art would expect other lipophilic and amphiphilic anesthetic agents to behave similarly to bupivacaine and would further expect a treatment effective for cardiotoxicity caused by bupivacaine to be applicable to cardiotoxicity caused by other anesthetic agents.

Applicants believe that the specification would enable one skilled in the art to practice and use the invention as defined in the amended claims, and that the scope of the amended claims are commensurate in scope with the disclosure provided.

The Office Action also rejected the claims under 35 U.S.C. 112, second paragraph, because the Examiner alleges it is unclear whether the emulsions are oil-in-water emulsions or water-in-oil emulsions. As amended, claim 27 recites that the lipid emulsion comprises at least 70% water by weight. One skilled in the art would recognize that an emulsion comprising 70% percent of water, or more, would be an oil-in-water emulsion.

In light of the above amendments and arguments, Applicants request that the rejections under 35 U.S.C. 112, be withdrawn.

II. Rejection under 35 U.S.C. 103

The Examiner also rejected the claims under 35 U.S.C. 103. The Examiner asserted that the claims were obvious in light of U.S. 4,183,918 (Asher) by itself, or Asher in combination with U.S. 4,323,563 (Takami) and U.S. 6,139,871 (Hope). Asher generally discloses lipid emulsions for the removal of toxins in the gastrointestinal tract.

As discussed above, claim 27 is amended to recite a method for treating cardiotoxicity caused by a toxic dose of an anesthetic agent. Asher does not teach or suggest lipid emulsions that can be generally used to treat cardiotoxicity, or, more specifically, cardiotoxicity caused by anesthetics. Similarly, no other prior art reference teaches that an animal or human patient suffering from cardiotoxicity caused by an anesthetic agent can be resuscitated through the administration of a lipid emulsion.

Furthermore, the lipid emulsions disclosed by Asher require an additional chemical reagent within the emulsion which reacts with or chemically modifies the toxin. In one embodiment disclosed by Asher, the interior of the emulsion comprises a reagent or adsorbent capable of converting said toxin into an innocuous or nonpermeable compound (abstract, and column 4, lines 5-17). In a second embodiment disclosed by Asher, the emulsion encompasses a catalyst, wherein reactants present in the GI tract permeate the emulsion and are converted into desired products by the catalyst (abstract, and column 4, lines 18-30). In a third embodiment disclosed by Asher, the emulsions are utilized as slow release drugs where the interior of the emulsion contains a drug that is slightly soluble in the exterior phase of the emulsion and is released over a period of time (abstract, and column 4, lines 31-39). In particular, the reagent in the interior of the emulsion is designed to convert the toxin into an innocuous or impermeable form (column 7, lines 36-45, examples of the interior reagent are given in Table 2). Examples 2-4 (columns 9-13) describe the removal of ammonia using a lipid

emulsion containing hydrochloric acid, the removal of urea using a lipid emulsion containing urease, and the removal of phosphate using a lipid emulsion containing calcium salts. In each case, the lipid emulsion is specifically designed to contain an additional chemical reagent to neutralize the target toxin. Asher does not teach or suggest an emulsion that is capable of removing any toxin without the additional chemical reagent. In contrast, the lipid emulsions of the present invention do not require the use of an additional reagent to remove or neutralize the anesthetic.

Claim 27 is amended to recite a lipid emulsion comprising essentially of an oil, an emulsifier, a tonicity modifier, and water. The phrase "consisting essentially of" limits the scope of a claim to specified materials recited in the claim (MPEP 2111.03). Thus, claim 27 as amended excludes the lipid emulsions described by Asher which must include additional chemical reagents to interact with the toxin. In situations where a patient's heart activity is impaired due to an anesthetic drug or compound, it is preferable to administer a treatment that can be applied as universally as possible and does not contain chemicals which may complicate the patient's status. A preferred composition is a lipid emulsion that is able to resuscitate a patient without additional chemical reagents. When developing a new treatment for cardiotoxicity caused by anesthetic agents, one skilled in the art would have no motivation to consider lipid emulsions containing additional chemical reagents specifically designed to remove toxins from the GI tract.

Furthermore, Asher also requires the use of non-digestible components to form the lipid emulsion in order to survive the GI tract. In particular, Asher specifically rejects oil components containing animal and vegetable oils and triglycerides because they are readily digestible (column 3, lines 20-30, column 4, lines 54-59). Claims 3-6 of the present invention recite that the lipid emulsion can comprise triglycerides, animal oils and vegetable oils. While such lipid emulsions are completely unsuitable for use in the GI tract as taught by Asher, they would be preferable in the present invention because they would be easily tolerated and removed by the body. Not only does Asher fail to

teach the present method of treating cardiotoxicity, Asher in fact teaches away from specific embodiments of the present invention.

In light of the above amendments and arguments, Applicants request that the obviousness rejections under 35 U.S.C. 103 be withdrawn.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested. If there are further issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by the Declaration of Dr. Guy Weinberg and a Petition for Extension of Time (three months). The Petition for Extension of Time authorizes the charge of $510.00 to Deposit Account No. 07-1969 as required under 37 C.F.R. §1.17. If that amount is incorrect, however, please charge said Deposit Account the amount required for this submission.

Respectfully submitted,

/michaeljcurtis/

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